September 17, 2003

Bruce Katje
Regulatory Compliance Manager
ESCO Company Limited Partnership
2340 Roberts Street
P.O. Box 448
Muskegon, MI 49443

Dear Mr. Katje:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Keto Acid Category posted on the ChemRTK HPV Challenge Program Web site on May 15, 2003. I commend ESCO Company Limited Partnership for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that ESCO advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
Keto Acids

SUMMARY OF EPA COMMENTS

The sponsor, ESCO Company Limited Partnership, submitted a test plan and robust summaries to EPA for Keto Acids dated April 25, 2003. EPA posted the submission on the ChemRTK HPV Challenge Web site on May 15, 2003. The submission includes 2-[4-(diethylamino)-2-hydroxybenzoyl]benzoic acid (EtKeto acid, CAS No. 5809-23-4) and 2-[4-(dibutylamino)-2-hydroxybenzoyl]benzoic acid (BuKeto acid, CAS No. 54574-82-2).

EPA has reviewed this submission and has reached the following conclusions:

1. Category Justification. The submitter's arguments for similarity of the chemicals are reasonable.

2. Physicochemical Properties. The submitter needs to (a) provide estimated boiling point data for EtKeto acid; (b) verify EtKeto vapor pressure values; and (c) provide detailed information on the method used for partition coefficient.

3. Environmental Fate. The submitter needs to provide quantitative biodegradation values and model input values for fugacity.

4. Health Effects. Adequate data are available for acute toxicity of EtKeto acid and BuKeto acid and for repeated-dose, genetic, reproductive and developmental toxicities of BuKeto acid for the purposes of the HPV Challenge Program. The submitter needs to address a few deficiencies in the robust summaries.

5. Ecological Effects. EPA reserves judgement on the adequacy of the acute toxicity data on fish, aquatic invertebrate, and aquatic plants pending receipt of critical data elements.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA COMMENTS ON THE KETO ACIDS CHALLENGE SUBMISSION

General

In Test Plan Conclusion on page 8, the submitter mentioned that keto acids are used as "closed system intermediates". However, the test plan does not include a formal claim of closed system intermediate status. The submitter may wish to clarify this statement.

The submitter needs to correct the typographic errors in tables in the test plan (on pages 1 and 2) and robust summaries (on page 1). The field "Color Former Name" should be replaced with "Keto Acid Name".

Category Definition

The submitter proposed a category of two N-alkyl derivatives of 2-[4-(amino)-2-hydroxybenzoyl]benzoic acid: 2-[4-(diethylamino)-2-hydroxybenzoyl]benzoic acid (EtKeto acid, CAS No. 5809-23-4) and 2-[4-(dibutylamino)-2-hydroxybenzoyl]benzoic acid (BuKeto acid, CAS No. 54574-82-2). The definition is clear and unambiguous.

(As a general matter, EPA prefers to apply the term "category" to groups of three or more chemicals. Such groups provide a range of endpoint data for similar chemicals that may allow one to identify trends and then use those trends to estimate missing data. On the other hand, extrapolation of data from one of

a pair of chemicals to the other, or analog assessment, requires a close and well-supported (not merely hypothetical) relationship between the two chemicals for each endpoint in question. For more on these topics see "Guidance for Development of Chemical Categories in the HPV Challenge Program" and "The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program", at www.epa.gov/chemrtk/guidocs.htm.)

Category Justification

The submitter bases the justification of the keto acid category on a similarity in chemical structure between the two compounds, which differ only in the length of the alkyl substituents on the amine function of the 2-hydroxybenzoyl group. The submitter anticipates that the close structural relationship between the two compounds will result in comparable physicochemical, environmental, and toxicological properties for EtKeto and BuKeto acids. EPA agrees that using BuKeto acid data to fill data gaps for EtKeto acid is reasonable except for some of the physicochemical endpoints.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

The data provided by the submitter for melting point, water solubility and partition coefficient are adequate for the purposes of the HPV Challenge Program.

Boiling point. In the robust summary, the submitter only indicates that these chemicals melt at temperatures above 201°C, and that no boiling point data have been generated. The submitter needs to provide quantitative boiling point data for these chemicals. The high melting points suggest that these chemicals boil or decompose at very high temperatures. OECD guidelines indicate that estimated values are accepted for chemicals whose estimated boiling point exceeds 300°C.

Vapor pressure. The submitter provided a vapor pressure of 13 Pa (0.098 mm Hg) at 20°C for BuKeto acid in the robust summaries. The submitter proposed a read-across approach for EtKeto acid. EPA found estimated vapor pressures of 1.76×10^{-10} and 1.47×10^{-11} mm Hg at 25°C for EtKeto and BuKeto acid, respectively (using MPBPWIN v1.40, melting points of 201 and 187°C were entered into MPBPWIN for the ethyl and butyl derivatives respectively).

There is a large discrepancy between the estimated vapor pressure obtained by EPA and the measured vapor pressure provided by the submitter. While the structures of the two category members are very similar, and it would be expected that they would have similar vapor pressures, this discrepancy indicates that there may be an error in the submitter's data for the BuKeto acid. Therefore, using the vapor pressure for BuKeto acid to satisfy the EtKeto acid endpoint may not be appropriate. The submitter needs to verify the value provided. According to OECD guidelines, calculations showing a value $<1 \times 10^{-5}$ Pa (7.5×10^{-8} mm Hg) at 25°C may be acceptable in lieu of measuring vapor pressure.

Partition coefficient. The submitter needs to provide detailed information on the method used and clearly indicate how the value for EtKeto acid will be related to that of BuKeto acid.

Water solubility. The submitter needs to state clearly how the water solubility for EtKeto acid will be related to that of BuKeto acid.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

The data provided by the submitter for photodegradation, stability in water and biodegradation are adequate for the purposes of the HPV Challenge Program.

Stability in water. The test plan states, "The photodegradation and hydrolysis endpoints for the keto acids were estimated with the EPA model, EPIWin...Very little of the keto acids dissolve in water, so hydrolysis is...not a very likely route of degradation." Hydrolysis of these chemicals is unlikely because the molecules contain no hydrolyzable functions. The test plan and robust summary should be revised to reflect this (a code of "NA" rather than "A" should appear in Table 1 of the test plan).

Biodegradation. The submitter's code of "C" rather than "A" should appear in Table 1 of the test plan.

Fugacity. The submitter needs to include the model input values in the robust summary for fugacity.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

Adequate data are available for acute toxicity of EtKeto acid and BuKeto acid and for repeated-dose, genetic, reproductive and developmental toxicities of BuKeto acid for the purposes of the HPV Challenge Program. The submitter's plan to use the data on BuKeto acid to satisfy data gaps for EtKeto acid is acceptable and is supported by the structural similarities between the two compounds. The submitter needs to address a few deficiencies in the robust summaries.

Developmental toxicity. The submitter needs to provide a separate robust summary describing developmental effects from the one-generation toxicity study on BuKeto acid.

Ecological Effects (fish, invertebrates, and algae)

No data on EtKeto acid were provided in the summary to satisfy any of the ecotoxicity endpoints. The test plan indicates that data for BuKeto acid will be used to satisfy the endpoints for EtKeto acid. This is acceptable given the structural similarity of the two chemicals. In addition, ECOSAR values calculated by EPA support the conclusion that BuKeto acid is expected to be more toxic than EtKeto acid. However, EPA reserves judgement on the adequacy of the fish, daphnia and algae studies pending receipt of critical missing data elements in the robust summaries (*see* Specific Comments on the Robust Summaries).

Specific Comments on the Robust Summaries

Generic comments

The submitter needs to state the purity of the test substance in all robust summaries.

Health Effects

Acute toxicity. Information missing from the robust summary of the acute oral toxicity study in rats exposed by gavage to EtKeto acid includes the dosing volume, the clinical signs observed and body weight effects (if measured).

Genetic toxicity. Robust summaries for a bacterial mutagenesis assay and an *in vitro* chromosomal aberration assay on BuKeto acid do not provide information on the number of replicates and number of metaphases examined.

Ecological Effects

Fish. Details missing include an adequate description of the test substance, water quality parameters (*e.g.*, pH, temperature, dissolved oxygen), guideline used, and an assigned reliability code.

Invertebrates. Details missing include an adequate description of the test substance, dose-response information, and water quality parameters (*e.g.*, pH, temperature, dissolved oxygen), guideline used, and an assigned reliability code.

Algae. Details missing include study type (*e.g.*, static, semi-static, flow-through), an adequate description of the test substance, dose-response information, and water quality parameters (*e.g.*, pH, temperature).

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.